Interpretive Guidance Document

for Producing

Sustainable Futures (SF) Summary Assessment

using

P2 Framework Models

This document was developed to help interpret results of US EPA OPPT's P2 Framework Models www.epa.gov/oppt/p2framework/ and is used by OPPT during Sustainable Futures (SF) training www.epa.gov/opptintr/newchems/sustainablefutures.htm.

Last Updated: January 2004

Table of Contents

PHYSICAL/CHEMICAL PROPERTIES AND ENVIRONMENTAL FATE

Entering Data into EPI Suite

The structure of the chemical is entered into EPI Suite in several ways:

- Enter CAS Registry Number and if the chemical is in the accompanying database the SMILES string for the structure is retrieved;
- Enter the SMILES notation; or
- Draw and save the structure as a MOL file in one of the free chemical drawing programs, such as ISISDraw or ChemDraw (both downloadable from the Internet), and import the MOL file.

Locate any experimental or measured data:

- Any available experimental data for the chemical should be entered into the input screen.
- For chemicals that are liquids at room temperature and have no experimental MP data, enter 20 deg C as the experimental MP into the input screen so that the program will know it is a liquid.

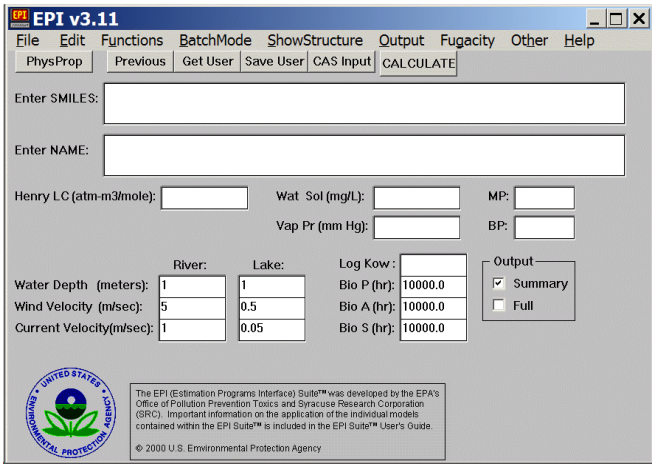

Figure 1. EPI Suite Data Input Screen

Interpreting Results for P/Chem Properties and Environmental Fate

Melting Point and Boiling Point - MPBPVP

MP < 25 deg C	Liquid
MP > 25 deg C	Solid
BP < 25 deg C	Gas

Vapor Pressure - MPBPVP

10^{-4}	Vapor (gas) phase
10^{-5} - 10^{-7}	Vapor and particulate phase
10^{-8}	Solid phase

For chemicals with a VP < 10^{-6}, there is low concern for inhalation exposure.

Water Solubility (mg/L) - WSKOWWIN

> 10,000	Very soluble
> 1,000 - 10,000	Soluble
> 100 - 1,000	Moderate solubility
> 0.1 - 100	Slightly soluble
< 0.1	Insoluble

Log K_{ow} (Log P) - KOWWIN

< 1	Highly soluble in water (hydrophilic)
> 4	Not very soluble in water (hydrophobic)
> 8	Not readily bioavailable
> 10	Not bioavailable - difficult to measure experimentally

Henry's Law Constant (atm-m^3/mole) - HENRYWIN

10^{-1}	Very volatile from water
10^{-1} - 10^{-3}	Volatile from water
10^{-3} - 10^{-5}	Moderately volatile from water
10^{-5} - 10^{-7}	Slightly volatile from water
< 10^{-7}	Nonvolatile

If experimental vapor pressure ***and*** water solubility data are available and entered as input data into EPI Suite, then the VP/Wsol estimate should be used instead of the bond or group estimation method.

Atmospheric Oxidation Half-life - AOPWIN

2 hours	Rapid
2 hrs - 1 day	Moderate
> 1 day - 10 days	Slow
>10 days	Negligible
>2 days	Has potential for long range transport in air

Hydrolysis Rates - HYDROWIN

HYDROWIN estimates Hydrolysis Rates only for Esters, Carbamates, Epoxides, Halomethanes, and certain Alkyl Halides.

Biodegradation - BIOWIN: 3 Models Available in EPI Suite

MODEL: Probability of Rapid Biodegradation (BIOWIN)	
BIOWIN Linear and BIOWIN Nonlinear	
> 0.50	Biodegrades Fast
< 0.50	Does Not Biodegrade Fast

MODEL: Expert Survey Biodegradation (Primary/Ultimate)	
Predicted Rating	**Time Required for Biodegradation**
5.0	Hours
4.5	Hours - days
4.0	Days
3.5	Days - weeks
3.0	Weeks
2.5	Weeks - months
2.0	Months
1.0	Longer

MODEL: Ready Biodegradability Model (MITI)	
MITI Linear and MITI Nonlinear	
>0.50	Ready Degradable
<0.50	Not Ready Degradable

Soil Adsorption Coefficient (Log K_{oc}) - PCKOWWIN

4.5	Very strong sorption to soil and sediment, negligible migration potential to groundwater
3.5 - 4.4	Strong sorption to soil and sediment, negligible to slow migration potential to groundwater
2.5 - 3.4	Moderate sorption to soil and sediment, slow migration potential to groundwater
1.5 - 2.4	Low sorption to soil and sediment, moderate migration potential to groundwater
< 1.5	Negligible sorption to soil and sediment, rapid migration potential to groundwater

Bioconcentration Factors - BCFWIN

> 5000	High bioconcentration potential
1000 - 5000	Moderate bioconcentration potential
< 1000	Low bioconcentration potential

STPWIN - Percent Removal in Sewage Treatment Plants

Gives an indication of the percent removed from biodegradation, sludge adsorption, and aeration in a POTW or Sewage Treatment Plant. Negligible biodegradation (half-life = 10,000 hours) is the default value for the primary clarifier (P), aeration vessel (A), and final settling tank (S) unless otherwise specified in the input screen for EPI Suite. If biodegradation data are available for the chemical, the defaults can be changed in the input screen, using

the following suggested values.

1 hour	For chemicals with data suggesting rapid biodegradation potential
3 hours	For chemicals with data suggesting moderate biodegradation potential
30 hours	For chemicals with data showing slow biodegradation potential
10,000 hours	Default rate for chemical with unknown biodegradation potential

LEV3EPI - Fugacity Model
Provides an indication of which environmental compartment the chemical is expected to partition to and calculates an approximate persistence time.

WVOL - Volatilization from Water
Uses molecular weight, Henry's Law Constant, and water solubility to estimate an ***upper*** limit for volatilization from a body of water. The model ***does not*** take into account potential adsorption to sediment and suspended organic matter when the K_{oc} is high, which can increase the volatilization half-life dramatically. Therefore, if the K_{oc} for a given chemical is high, the volatilization half-lives from a model river and model lake are expected to be significantly higher than as predicted in WVOL.

HAZARD ESTIMATION

Aquatic Toxicity Hazard - ECOSAR

Develop Full Standard Aquatic Toxicity Profile
The standard aquatic toxicity profile consists of 3 acute values (fish LC_{50}, Daphnid LC_{50}, and algae EC_{50}) and 3 chronic values (fish ChV, Daphnid ChV, and algal ChV). Examples of toxicity values that are generally used to complete a standard aquatic toxicity profile are provided below.

Organism	Acute Toxicity Values	Chronic Toxicity Values
Fish	96-hour LC_{50}	30-day ChV
Daphnid*	48-hour LC_{50}	ChV or 16-day EC_{50}
Algae	72 or 96-hour EC_{50}	ChV

*Aquatic invertebrate

A full standard profile for each chemical should be produced using either predicted or experimental data. If no predicted or experimental data are available for the chemical of interest, then analog data may be used. If a single measured or predicted toxicity value is available for a species but the corresponding acute or chronic value is not, then an Acute to Chronic Ratio (ACR) can be used to estimate the corresponding acute or chronic toxicity value:

Chronic toxicity estimate = (acute toxicity value) / (ACR)
Acute toxicity estimate = (chronic toxicity value) x (ACR)

An ACR of 10 is commonly applied to fish and Daphnids and an ACR of 4 is commonly applied to algae. Example calculations are provided below.Ecological Assessment of Polymers: Strategies for Product Stewardship and Regulatory Programs

Fish LC_{50} = 0.10 mg/L â extrapolated fish ChV = (0.10 mg/L)/10 = 0.01 mg/L (ppm)
Algal ChV = 0.02 mg/L â extrapolated algal EC_{50} = (0.02 mg/L) x 4 = 0.08 mg/L (ppm)

A full toxicity profile needs to be developed to perform an aquatic toxicity assessment. If an acute or chronic toxicity endpoint cannot be determined for one or more species from measured data on the chemical or analog or from predicted data, category data can be used to fulfill the endpoint. For example, a fish or Daphnid toxicity value can be estimated using the fish-to-Daphnid toxicity ratio specific to chemicals within the same category (e.g., acrylates). Use data from multiple chemicals if possible. All assumptions and toxicity data used for the estimation need to be documented in the Sustainable Futures Summary Assessment.

The following guidance can be used to assign aquatic toxicity concern levels.

High	Any of the 3 acute values are <1 mg/L, OR any of the chronic values are <0.1 mg/L
Moderate	Any of the 3 acute values are >1 mg/L and <100 mg/L, OR any of the chronic values are >0.1 mg/L and <10.0 mg/L
Low	All 3 acute values are >100 mg/L, AND all three chronic values are >10.0 mg/L, or there are "No Effects at Saturation" (NES). NES occurs when the water solubility of the chemical is higher than an effect concentration -or- when the K_{ow} criteria are exceeded for an endpoint for liquid chemicals. For solid chemicals, NES is expected if the K_{ow} criteria are exceeded for a chemical, or the effect concentration is 10x above the water solubility.

NOTES:

- K_{ow} cut-offs are specific for each SAR, and can be found at the bottom of the ECOSAR results screen or in the ECOSAR User's Manual.
- Guidance on the evaluation of polymers can be found in: Boethling R.S. and J.V. Nabholz. 1997. "Environmental assessment of polymers under the U.S. Toxic Substances Control Act", Chap. 10 In: Hamilton, J.D. and R. Sutcliffe, eds. Ecological Assessment of Polymers: Strategies for Product Stewardship and Regulatory Programs. New York, NY: Van Nostrand Reinhold, 187-234. ISBN 0-471-28782-2.

Human Health Hazard - Cancer

Interpreting Results from Cancer Expert System

Concern	OncoLogic Result	Definition - OncoLogic Result
Low	Low	Unlikely to be a carcinogen
Further Research Needed	Marginal	Likely to have equivocal carcinogenic activity
Moderate	Low-Moderate	Likely to be weakly carcinogenic
	Moderate	Likely to be moderately active carcinogen
High	Moderate-High	Highly likely to be a moderately active carcinogen
	High	Highly likely to be a potent carcinogen

Interpreting Experimental Data

Concern	Definition - Experimental Data
Low	Negative experimental data
Moderate	Positive cancer bioassay in animals ***- or -*** chemical class known to produce carcinogenic effects
High	Positive experimental data in humans (e.g. epidemiology study)

NOTE: Experimental data on the chemical, or a close analog, take precedence over predicted data.

Human Health Hazard - Non-Cancer

Criteria for Assigning Non-Cancer Hazard Concern Levels

Concern	Definition - Experimental Data
Low	No concern identified
Moderate	Suggestive animal studies for chemical or analog(s) ***- or -*** chemical class known to produce toxicity
High	Evidence of adverse effects in humans ***- or -*** conclusive evidence of severe effects in animal studies

Regulatory decisions will be made based on the following effects:

- Reproductive Effects
- Immune Effects
- Developmental Effects
- Neurotoxicity
- Systemic Effects

NOTE: Guidance on the evaluation of high molecular weight polymers in EPA's New Chemicals Program is summarized in Appendix F of the *P2 Framework Manual*, January 2003 http://www.epa.gov/oppt/p2framework/ The information is summarized from http://www.epa.gov/opptintr/newchems/hmwtpoly.htm

EXPOSURE ESTIMATION

Aquatic Exposure - E-FAST

Predicted Environmental Concentration (PEC)
Amount expected to be found in surface water after release from industrial processes; also called surface water concentration (SWC).

Estimated values can be determined using **E-FAST** and are found under the "General SIC Code Information" tab in the results screen. The **10% percentile, 7Q10 stream concentrations (µg/L)** are the most conservative and used for an SF Assessment.

To run E-FAST you will need to determine a chronic **Concentration of Concern (COC)** based on the toxicity values derived in the Aquatic Toxicity section. The COC is one of the inputs for the E-FAST program and an explanation for the determination of a chronic COC can be found on the following page of this document.

Human Exposure - ChemSTEER and E-FAST

Occupational Exposure Doses
LADD, ADD, and APDR values will be estimated by **ChemSTEER**

General Population Exposure Doses
LADDpot, ADDpot, and ADRpot values will be estimated by **E-FAST.** The **10% percentile values (mg/kg/day)** are used for an SF Assessment.

Lifetime Average Daily Dose (LADD or LADDpot)
The predicted lifetime exposure used to determine cancer risk usually based on an average lifetime of 70 - 75 years and a working lifetime of 30 - 40 years.

Potential Average Daily Dose (ADD or ADDpot)
The predicted dose that represents potential chronic exposure based on a duration of repeated exposure usually approximating an average of 30 years.

Potential Acute Dose Rate (APDR or ADRpot)
The predicted acute dose rate that represents acute exposure usually based on a single 8 hour working day exposure duration.

NOTE: For the purposes of an SF Assessment, the defaults for average lifetime, body weight, exposure duration, and ingestion rate are pre-set in both ChemSTEER and E-FAST and should not be changed unless specific data for these inputs are available.

RISK ESTIMATION

RISK = HAZARD x EXPOSURE*
The National Academy of Science defined risk as hazard (toxicity) times exposure. For chemicals with an identified hazard concern, the potential exposure must be determined to make an assessment of risk. If no hazard is identified (hazard = 0) or no exposure is identified (exposure = 0), then there is low concern for risk (risk = 0).
*NRC. 1983. Risk Assessment in the Federal Government: Managing the Process. National Research Council. National Academy Press, Washington, DC. ISBN: 0-309-03349-7.

Estimating Aquatic Risk

Determine Acute and Chronic Concentration of Concern (COC)
Concentration at which potential acute or chronic aquatic toxicity may be of concern for aquatic species.

Acute COC
Acute COC for fish and Daphnids = (lowest LC_{50} or EC_{50}) / (5)
Acute COC for algae = (EC_{50}) / (4) - OR - If an algal ChV value exists, use that value as the acute COC and do not estimate the COC using an EC_{50} value divided by a factor.

Chronic COC
Chronic COC = (lowest ChV) / (10)

Example calculations are provided below:

Fish LC_{50} = 0.10 mg/L â calculated Acute COC = (0.10 mg/L) /5 = 0.02 mg/L (ppm)
Daphnid ChV = 0.02 mg/L â calculated Chronic COC = (0.02 mg/L) /10 = 0.002 mg/L (ppm)

Calculate a COC for every species in the full profile and use the lowest acute and chronic values determined as the acute and chronic COC.

NOTES:
- All COCs are rounded up to 1 significant digit, (e.g., a COC of 1.75 ppb is rounded up to 2 ppb).
- All COC values less than 1 ppb are rounded up to 1 ppb for an SF Assessment. No values less than 1 ppb (the detection limit) should be reported.

Estimating Acute Aquatic Risk

The potential for acute risk to aquatic organisms exists if the acute concentration of concern (COC) is greater than the predicted environmental concentration (PEC).

If Acute COC > PEC Low concern for risk If Acute COC < PEC Potential for risk

Estimating Chronic Aquatic Risk

The potential for chronic risk to aquatic organisms may exist if the COC is exceeded for 20 days or more per year. If not exceeded for 20 days or more, then there is low concern for risk.

E-FAST will predict how many days per year the (PEC) exceeds the (COC). The number of days the COC is exceeded can be found on the “PDM SIC” tab in the output screen of E-FAST.

The 20-day criterion is derived from partial life-cycle tests (Daphnid chronic and fish early life-stage tests) that typically range from 21 to 28 days in duration. Low concern for chronic risk exists if the COC is exceeded on fewer than 20 days.

Example Worksheet for Estimating Aquatic Acute and Chronic Risk

ECOSAR predicted the values below for the Example Chemical # 1 used during the Sustainable Futures training sessions. This chemical is 1,2-dichloro-4-nitro-5-pentylbenzene (no CAS RN identified). The structure is shown in Figure 2.

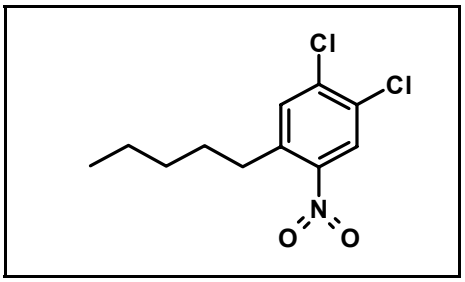

Figure 2.
1,2-dichloro-4-nitro-5-pentylbenzene

Acute Endpoint	Value	Factor	Acute COC
Fish LC50	0.079 ppm	5	0.02 ppm
Daphnid LC50	0.11 ppm	5	0.02 ppm
Algae EC50	0.083 ppm	4	0.07* ppm

* Since an algal ChV value was available (see below), the ChV value was used as the algal acute COC.

Chronic Endpoint	Value	Factor	Chronic COC
Fish ChV	0.018	10	0.002 ppm
Daphnid ChV	0.027	10	0.003 ppm
Algae ChV	0.067	10	0.007 ppm

Acute COC = 0.02 ppm based on the fish and Daphnid acute values
Chronic COC = 0.002 ppm based on the fish ChV value
PEC = 0.055 ppm
PEC exceeds the COC for 9.4 days per year

CONCLUSIONS: There is **potential for acute risk** because the PEC is greater than the acute COC. There is **low concern for chronic risk** because even though the PEC exceeds the chronic COC, it is only exceeded for 9.4 days.

Human Health Risk - Non-Cancer

Estimating Acute Risk to the General Population Using the Margin of Exposure (MOE)

NOTES:
- When acute toxicity studies indicate LD_{50} values > 50 mg/kg, there is no need to calculate an MOE for acute exposure and a low concern for acute risk is assumed.
- There is potential acute hazard concern if the LD_{50} < 50 mg/kg. An MOE needs to be calculated and the potential for acute risk to the general population needs to be assessed when acute toxicity studies with LD_{50} values < 50 mg/kg have been identified.

MOE based on Acute Exposure Value
Ratio of the identified effect level (LD_{50} value determined in health hazard section) to the estimated acute dose rate (predicted from E-FAST).

$$MOE_{acute} = LD_{50} \text{ (mg/kg)} / \text{ADRpot (from E-FAST)}$$

MOE < 1000 indicates potential for risk MOE > 1000 indicates low concern for risk

Estimating Chronic Human Health Risk Using the MOE

Regulatory decisions will be made based on the following effects:

- Reproductive Effects
- Immune Effects
- Developmental Effects
- Neurotoxicity
- Systemic Effects

MOE based on Chronic Exposure Value

An MOE is the ratio of the No-Observed Adverse-Effect-Level (NOAEL) or the Lowest-Observed Adverse-Effect-Level (LOAEL) for the effect (determined in health hazard section) to the estimated exposure value (predicted from exposure models). If both a NOAEL and LOAEL are available, use the NOAEL value to calculate the MOE.

$MOE_{, \text{Occupational}}$ = NOAEL or LOAEL (Non-Cancer) / APDR or ADD (from ChemSTEER)

$MOE_{, \text{General Population}}$ = NOAEL or LOAEL (Non-Cancer) / ADRpot or ADDpot (from E-FAST)

The following table shows the human health non-cancer endpoints and the corresponding acute/chronic exposure values to use for calculation of an MOE.

Endpoint	Exposure Dose
Single Dose Studies	
Acute Toxicity	ADRpot (acute)*
Repeated Dose Studies	
Irritation	Cannot be used to determine MOE
Skin Sensitizer	Cannot be used to determine MOE
Reproductive Effects	ADDpot (chronic)
Immune System Effect	ADDpot (chronic)
Developmental Toxicity	ADRpot (acute)
Genotoxicity	Cannot be used to determine MOE
Mutagenicity	Cannot be used to determine MOE
Neurotoxicity	ADDpot (chronic)
Systemic Effects	ADDpot (chronic)
*Acute risk is assessed ONLY when an LD_{50} value < 50 mg/kg is identified for a chemical.	

If data for ANY of these effects indicate a moderate or high hazard concern, MOE for each moderate/high concern-endpoint should be determined. The lowest MOE value calculated will be used to determine the potential risk.

There is a potential risk concern for chemicals with an MOE < 100 based on studies with NOAEL values and for chemicals with MOE < 1000 based on studies with only LOAEL values. The preference is to identify a NOAEL value and use that value for your MOE calculations. The average daily dose (ADD or ADDpot) is used to determine an MOE with one exception; an MOE for developmental toxicity is based on the acute dose rate (APDR or ADRpot).

For Calculation based on NOAEL:
MOE < 100 indicates potential for risk
MOE > 100 indicates low concern for risk

For Calculation based on LOAEL:
MOE < 1000 indicates potential for risk
MOE > 1000 indicates low concern for risk

For MOE values based on **developmental toxicity data** a body weight of 60 kg should be used as input when determining the exposure values (ADD, ADR, LADD) instead of the default of 70 kg because developmental toxicity is only assessed in females. The assumption is that the average female body weight is less than that of a male.

Example Worksheet for Estimating Acute and Chronic Human Health Risk Potential Based on Non-Cancer MOE

E-FAST and ChemSTEER predicted the values below for the Example Chemical # 2 used during the Sustainable Futures training sessions. This chemical is 1-methyl-3-(2-methylpropyl)-cyclohexanol with a CAS RN of 215231-33-7. The structure is shown in Figure 3.

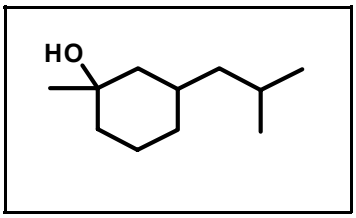

Figure 3.
1-methyl-3-(2-methylpropyl)-cyclohexanol

Type	Effect	NOAEL	LOAEL	Exposure	MOE
Occupational	Systemic	40 mg/kg-d	200 mg/kg-d	1.8×10^{-2} mg/kg-d ChemSTEER ADD	2222
	Neurotox	40 mg/kg-d	200 mg/kg-d	1.8×10^{-2} mg/kg-d ChemSTEER ADD	2222
General Population	Systemic	40 mg/kg-d	200 mg/kg-d	2.1×10^{-6} mg/kg-d E-FAST ADDpot	1.9×10^{7}
	Neurotox	40 mg/kg-d	200 mg/kg-d	2.1×10^{-6} mg/kg-d E-FAST ADDpot	1.9×10^{7}

The MOE to evaluate Risk from Occupational Exposure = 2222
The MOE to evaluate Risk from General Population Exposure = 1.9×10^{7}

CONCLUSIONS: There is **low concern for risk to Human Health** from both occupational exposure and exposure to the general population because all Margins of Exposure are greater than 100.

Human Health Risk - Cancer

NOTE: For the purposes of a Sustainable Futures Summary Assessment, a human health cancer risk assessment will not be required.

General Overview of a Cancer Risk Assessment

Occupational Exposure Doses
LADD will be calculated by ChemSTEER

General Population Exposure Doses
LADDpot will be calculated by E-FAST

Slope Factor = Slope Factor $(mg/kg\text{-}day)^{-1}$ (Calculated)

The Slope Factor is a measure of an individual's increased risk (i.e., increased likelihood) of developing cancer for each incremental increase in exposure to a chemical. It approximates the upper bound of the slope of the dose-response curve using the linearized multistage procedure at low doses. The calculation of a slope factor requires tools that are not provided in the P2 Framework. One such tool to calculate Slope Factors is the Benchmark Dose Software (BMDS) which can be downloaded from http://cfpub.epa.gov/ncea.

Cancer Risk = LADD or LADDpot x Slope Factor

Generally, a cancer risk of $> 1x10^{-6}$ (1 in 1,000,000) for the general population and $> 1x10^{-5}$ (1 in 100,000) for worker exposure indicates the potential for risk.